NOVOLOG MIX 70/30 - insulin aspart injection, suspension
Novo Nordisk

DESCRIPTION

NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin]) is a human insulin analog suspension containing 70% insulin aspart protamine crystals and 30% soluble insulin aspart. NovoLog® Mix 70/30 is a blood glucose-lowering agent with a rapid onset and an intermediate duration of action. Insulin aspart is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast) as the production organism. Insulin aspart (NovoLog®) has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8 Da.
Structural formula:

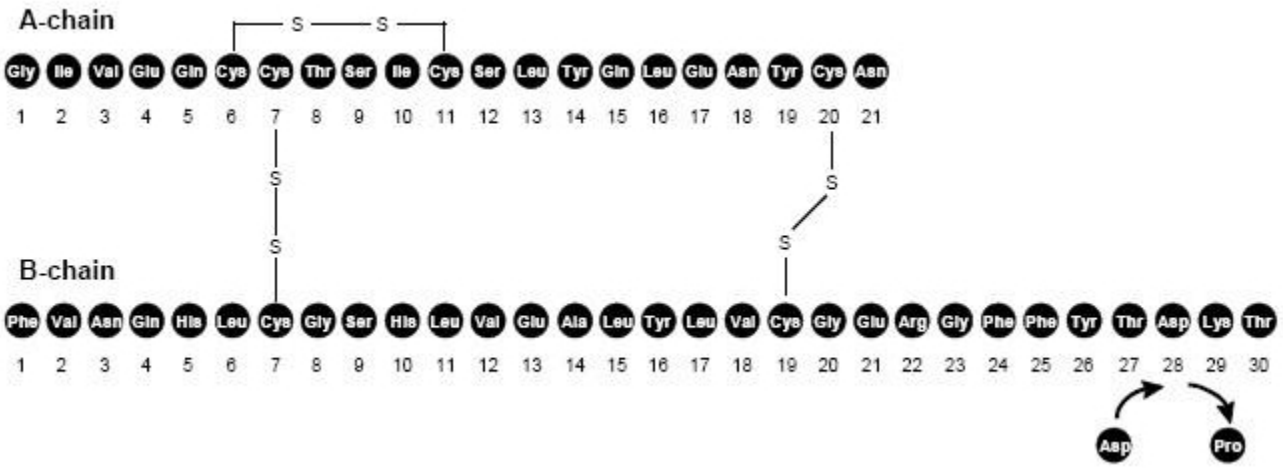

Figure 1. Structural formula of insulin aspart

NovoLog® Mix 70/30 is a uniform, white, sterile suspension that contains insulin aspart (B28 asp regular human insulin analog) 100 Units/mL.
Inactive ingredients for the 10 mL vial are mannitol 36.4 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 μg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, sodium chloride 0.58 mg/mL, and protamine sulfate 0.32 mg/mL. Inactive ingredients for the NovoLog® Mix 70/30 FlexPen® prefilled syringe are glycerol 16.0 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 μg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, sodium chloride 0.877 mg/mL, and protamine sulfate 0.32 mg/mL.
NovoLog® Mix 70/30 has a pH of 7.20 - 7.44. Hydrochloric acid or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY

Mechanism of action

The primary activity of NovoLog® Mix 70/30 is the regulation of glucose metabolism. Insulins, including NovoLog® Mix 70/30, exert their specific action through binding to insulin receptors. Insulin binding activates mechanisms to lower blood glucose by facilitating cellular uptake of glucose into skeletal muscle and fat, simultaneously inhibiting the output of glucose from the liver.
In standard biological assays in mice and rabbits, one unit of NovoLog® has the same glucose-lowering effect as one unit of regular human insulin. However, the effect of NovoLog® Mix 70/30 is more rapid in onset compared to Novolin® (human insulin) 70/30 due to its faster absorption after subcutaneous injection.

Pharmacokinetics

Bioavailability and Absorption
The single substitution of the amino acid proline with aspartic acid at position B28 in insulin aspart (NovoLog®) reduces the molecule's tendency to form hexamers as observed with regular human insulin. The rapid absorption characteristics of NovoLog® are maintained by NovoLog® Mix 70/30. The insulin aspart in the soluble component of NovoLog® Mix 70/30 is absorbed more rapidly from the subcutaneous layer than regular human insulin. The remaining 70% is in crystalline form as insulin aspart protamine which has a prolonged absorption profile after subcutaneous injection.

The relative bioavailability of NovoLog® Mix 70/30 compared to NovoLog® and Novolin® 70/30 indicates that they are absorbed to similar degrees. In euglycemic clamp studies in healthy volunteers (n=23) after dosing with 0.2 U/kg of NovoLog® Mix 70/30, a mean maximum serum concentration (C_{max}) of 23.4 ± 5.3 mU/L was reached after 60 minutes. The mean half-life (t1/2) of NovoLog® Mix 70/30 was about 8 to 9 hours. Serum insulin levels returned to baseline 15 to 18 hours after a subcutaneous dose. Similar data were seen in a separate euglycemic clamp study in healthy volunteers (n=24) after dosing with 0.3 U/kg of NovoLog® Mix 70/30. A C_{max} of 61.3 ± 20.1 mU/L was reached after 85 minutes. Serum insulin levels returned to baseline 12 hours after a subcutaneous dose.

The C_{max} and the area under the insulin concentration-time curve (AUC) after administration of NovoLog® Mix 70/30 differed by approximately 20% from those after administration of NovoLog® Mix 50/50 (investigational drug, not marketed) and Novolin® 70/30 (see Fig. 2 and 3 for pharmacokinetic profiles).

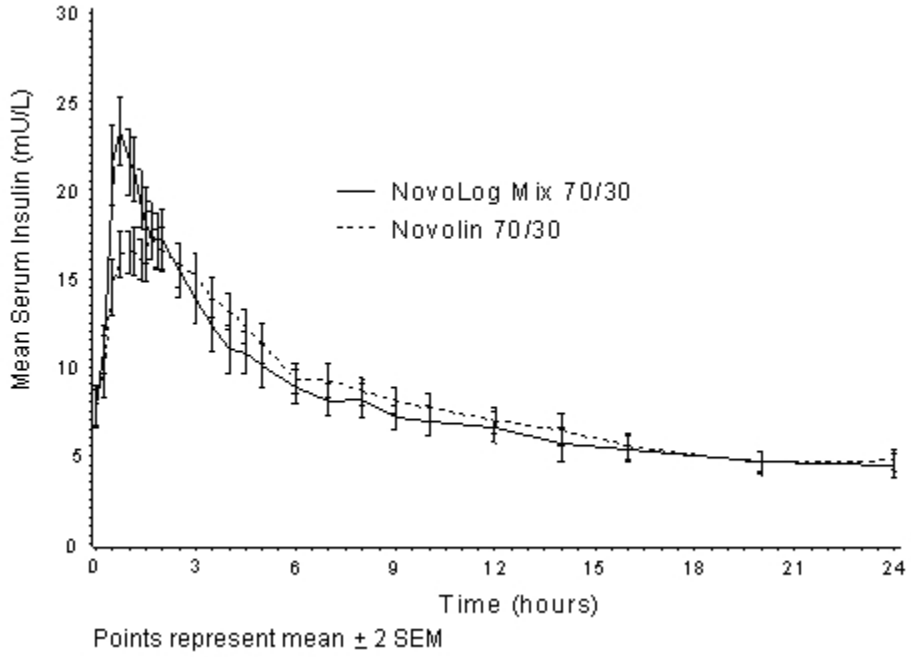

Figure 2. Pharmacokinetic Profiles of NovoLog® Mix 70/30 and Novolin® 70/30

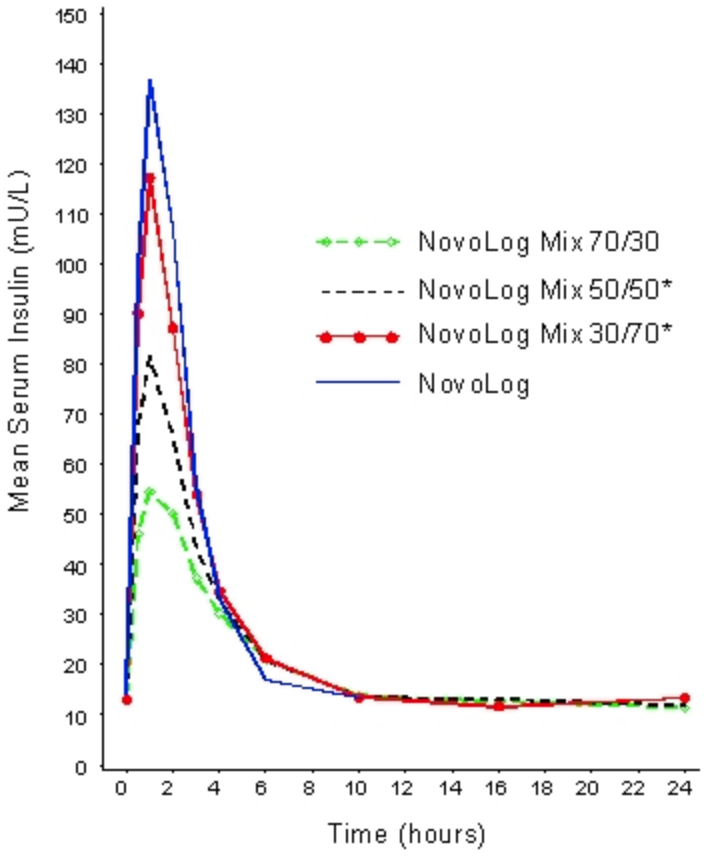

Figure 3. Pharmacokinetic profiles for NovoLog® Mix 70/30 and other proportional mixes (* investigational drugs, not marketed).

Pharmacokinetic measurements were generated in clamp studies employing insulin doses of 0.3 U/kg. Insulin kinetics exhibit significant inter- and intra-patient variability. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General). Differences in pharmacokinetics between NovoLog® Mix 70/30 and products to which it has been compared are not associated with differences in overall glycemic control.

Distribution and Elimination- NovoLog® has a low binding to plasma proteins, 0 to 9%, similar to regular human insulin. After subcutaneous administration in normal male volunteers (n=24), NovoLog® was more rapidly eliminated than regular human insulin with an average apparent half-life of 81 minutes compared to 141 minutes for regular human insulin.

Pharmacodynamics

The two euglycemic clamp studies described above assessed glucose utilization after dosing of healthy volunteers. NovoLog® Mix 70/30 has a more rapid onset of action than regular human insulin in studies of normal volunteers and patients with diabetes. The peak pharmacodynamic effect of NovoLog® Mix 70/30 occurs between 1 and 4 hours after injection. The duration of action may be as long as 24 hours (see Figures 4 and 5).

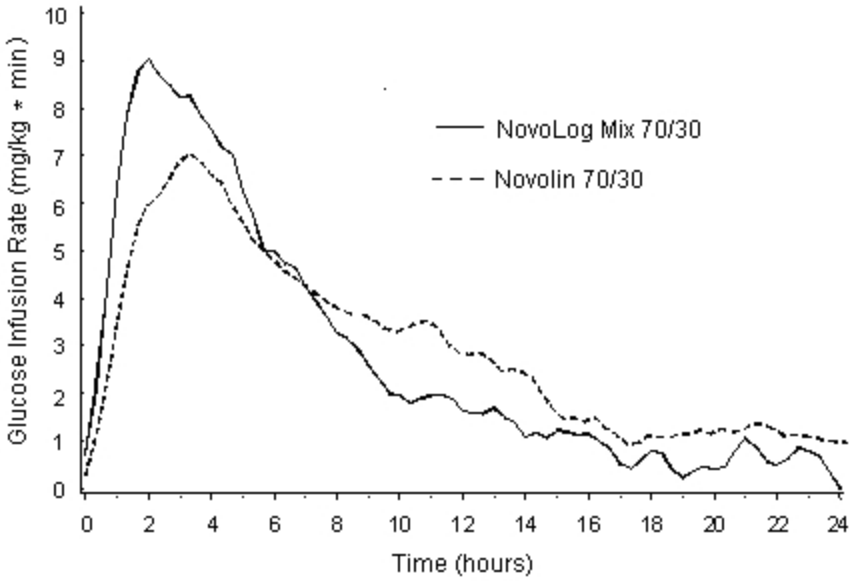

Figure 4. Pharmacodynamic Activity Profile of NovoLog® Mix 70/30 and Novolin® 70/30 in healthy subjects.

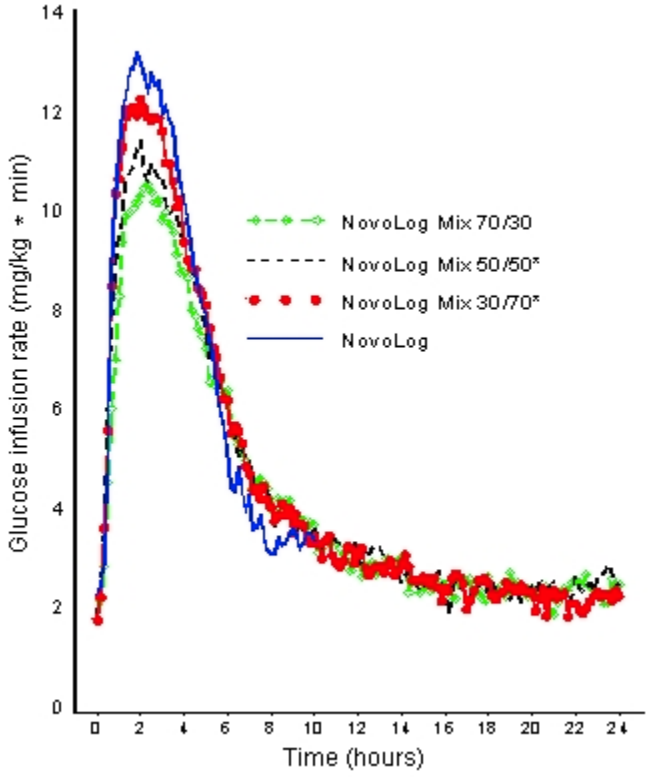

Figure 5. Pharmacodynamic Activity Profiles for NovoLog® Mix 70/30 and other proportional mixes (* investigational drugs, not marketed)

Pharmacodynamic measurements were generated in clamp studies employing insulin doses of 0.3 U/kg. Insulin pharmacodynamics exhibit significant inter- and intra-patient variability. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables (see PRECAUTIONS, General). Differences in pharmacodynamics between NovoLog® Mix 70/30 and products to which it has been compared are not associated with differences in overall glycemic control.

Special populations

Children and adolescents-The pharmacokinetic and pharmacodynamic properties of NovoLog® Mix 70/30 have not been assessed in children and adolescents less than 18 years of age.

Geriatrics-The effect of age on the pharmacokinetics and pharmacodynamics of NovoLog® Mix 70/30 has not been studied.

Gender- The effect of gender on the pharmacokinetics and pharmacodynamics of NovoLog® Mix 70/30 has not been studied.

Obesity-The effect of obesity and/or subcutaneous fat thickness on the pharmacokinetics and pharmacodynamics of NovoLog® Mix 70/30 has not been studied but data on the rapid acting component (NovoLog®) show no significant effect.

Ethnic origin-The effect of ethnic origin on the pharmacokinetics and pharmacodynamics of NovoLog® Mix 70/30 has not been studied.

Renal impairment-The effect of renal function on the pharmacokinetics and pharmacodynamics of NovoLog® Mix 70/30 has not been studied but data on the rapid acting component (NovoLog®) show no significant effect. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Careful glucose monitoring and dose adjustments of insulin, including NovoLog® Mix 70/30, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment).

Hepatic impairment- The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of NovoLog® Mix 70/30 has not been studied but data on the rapid-acting component (NovoLog®) show no significant effect. Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including NovoLog® Mix 70/30, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

Pregnancy-The effect of pregnancy on the pharmacokinetics and pharmacodynamics of NovoLog® Mix 70/30 has not been studied (see PRECAUTIONS, Pregnancy).

Smoking-The effect of smoking on the pharmacokinetics and pharmacodynamics of NovoLog® Mix 70/30 has not been studied.

CLINICAL STUDIES

In a three-month, open-label trial, patients with Type 1 (n=146) or Type 2 (n=178) diabetes were treated BID (before breakfast and before supper) with NovoLog® Mix 70/30 or Novolin® 70/30. The small changes in HbA1c were comparable across the treatment groups (see Table 1).

Table 1: Glycemic Parameters at the End of Treatment [Mean (SD)]

	NovoLog® Mix 70/30	**Novolin® 70/30**
Type 1, N=92		
Fasting Blood Glucose (mg/dL)	173 (62)	141 (59)
1.5 Hour Post Breakfast	185 (80)	198 (80)
1.5 Hour Post Dinner	158 (77)	169 (66)
HbA_{1c} (%)	8.4 (1.1)	8.3 (1.0)
Type 2, N=169		
Fasting Blood Glucose (mg/dL)	151 (39)	151 (68)
1.5 Hour Post Breakfast	180 (64)	198 (80)
1.5 Hour Post Dinner	166 (50)	189 (50)
HbA_{1c} (%)	7.9 (1.0)	8.1 (1.1)

The significance, with respect to the long-term clinical sequelae of diabetes, of the differences in postprandial hyperglycemia between treatment groups has not been established.

Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in the 3-month, open-label comparator trial as well as in a long-term extension trial (see PRECAUTIONS, Allergy).

In a 28-week, open-label trial, insulin-naïve patients with type 2 diabetes with fasting plasma glucose above 140 mg/dL currently treated with metformin ± thiazolidinedione therapy were randomized to receive either NovoLog® Mix 70/30 twice daily [before breakfast and before supper] or basal (long acting) insulin analog once daily[1] (see Table 2). NovoLog® Mix 70/30 was started at an average dose of 5-6 IU (0.07 ± 0.03 IU/kg) twice daily (before breakfast and before supper), and bedtime basal (long acting) insulin analog was started at 10-12 IU (0.13 ± 0.03 IU/kg). Insulin doses were titrated weekly by decrements or increments of -2 to +6 units per injection to a pre-meal glucose goal of 80-110 mg/dL. The metformin dose was adjusted to 2550 mg/day. Approximately one-third of the patients in each group were also treated with pioglitazone (30 mg/day). Insulin secretagogues were discontinued in order to reduce the risk of hypoglycemia. Most patients were Caucasian (53%), and the mean initial weight was 90 kg.

Table 2: Combination Therapy with Oral Agents and Insulin In Patients with Type 2 Diabetes Mellitus [Mean (SD)]

Treatment duration 28-weeks	**NovoLog® Mix 70/30**	**Basal (Long Acting) Insulin Analog**
Number of patients	117	116
HbA_{1c}		
Baseline mean (%)	9.7 (1.5)	9.8 (1.4)
End-of-study mean (± SD)	6.9 (1.2)	7.4 (1.2)
Mean change from baseline	-2.8	-2.4
Percentage of subjects reaching HbA_{1c} <7.0%	66%	40%
Total Daily Insulin Dose at end of study (U)	79 (40)	51 (27)
Number of patients with severe hypoglycemia	0	0
Minor hypoglycemic event/month/patient	0.28	0.06
Weight gain at end of study	5.4 (4.8)	3.5 (4.5)

INDICATIONS AND USAGE

NovoLog® Mix 70/30 is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

CONTRAINDICATIONS

NovoLog® Mix 70/30 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog® Mix 70/30 or one of its excipients.

WARNINGS

Because NovoLog® Mix 70/30 has peak pharmacodynamic activity one hour after injection, it should be administered with meals.

NovoLog® Mix 70/30 should not be administered intravenously.

NovoLog® Mix 70/30 is not to be used in insulin infusion pumps.

NovoLog® Mix 70/30 should not be mixed with any other insulin product.

Hypoglycemia is the most common adverse effect of insulin therapy, including NovoLog® Mix 70/30. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.

Needles and NovoLog Mix 70/30 FlexPen must not be shared.

PRECAUTIONS

General

Hypoglycemia and hypokalemia are among the potential clinical adverse effects associated with the use of all insulins. Because of differences in the action of NovoLog® Mix 70/30 and other insulins, care should be taken in patients in whom such potential side effects might be clinically relevant (e.g., patients who are fasting, have autonomic neuropathy, or are using potassium-lowering drugs or patients taking drugs sensitive to serum potassium level).

Fixed ratio insulins are typically dosed on a twice daily basis, i.e., before breakfast and supper, with each dose intended to cover two meals or a meal and snack (see DOSAGE AND ADMINISTRATION). The dose of insulin required to provide adequate glycemic control for one of the meals may result in hyper- or hypoglycemia for the other meal. The pharmacodynamic profile may also be inadequate for patients (e.g. pregnant women) who require more frequent meals.

Adjustments in insulin dose or insulin type may be needed during illness, emotional stress, and other physiologic stress in addition to changes in meals and exercise.

The pharmacokinetic and pharmacodynamic profiles of all insulins may be altered by the site used for injection and the degree of vascularization of the site. Smoking, temperature, and exercise contribute to variations in blood flow and insulin absorption. These and other factors contribute to inter- and intra-patient variability.

Lipodystrophy and hypersensitivity are among other potential clinical adverse effects associated with the use of all insulins.

Hypoglycemia

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of NovoLog® Mix 70/30. Rapid changes in serum glucose concentrations may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose

value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Renal Impairment

Clinical or pharmacology studies with NovoLog® Mix 70/30 in diabetic patients with various degrees of renal impairment have not been conducted. As with other insulins, the requirements for NovoLog® Mix 70/30 may be reduced in patients with renal impairment.

Hepatic Impairment

Clinical or pharmacology studies with NovoLog® Mix 70/30 in diabetic patients with various degrees of hepatic impairment have not been conducted. As with other insulins, the requirements for NovoLog® Mix 70/30 may be reduced in patients with hepatic impairment.

Allergy

Local Reactions- Erythema, swelling, and pruritus at the injection site have been observed with NovoLog® Mix 70/30 as with other insulin therapy. Reactions may be related to the insulin molecule, other components in the insulin preparation including protamine and cresol, components in skin cleansing agents, or injection techniques.
Systemic Reactions- Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening. Localized reactions and generalized myalgias have been reported with the use of cresol as an injectable excipient

Antibody production

Specific anti-insulin antibodies as well as cross-reacting anti-insulin antibodies were monitored in the 3-month, open-label comparator trial as well as in a long-term extension trial. Changes in cross-reactive antibodies were more common after NovoLog® Mix 70/30 than with Novolin® 70/30 but these changes did not correlate with change in HbA1c or increase in insulin dose. The clinical significance of these antibodies has not been established. Antibodies did not increase further after long-term exposure (>6 months) to NovoLog® Mix 70/30.

Information for patients

Patients should be informed about potential risks and advantages of NovoLog® Mix 70/30 therapy including the possible side effects. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction for use of injection devices, and proper storage of insulin.
Female patients should be advised to discuss with their physician if they intend to, or if they become, pregnant because information is not available on the use of NovoLog® Mix 70/30 during pregnancy or lactation (see PRECAUTIONS, Pregnancy).

Laboratory tests

The therapeutic response to NovoLog® Mix 70/30 should be assessed by measurement of serum or blood glucose and glycosylated hemoglobin.

Drug interactions

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring. The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g. octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin.

Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medical products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent (see CLINICAL PHARMACOLOGY).

Mixing of insulins

NovoLog® Mix 70/30 should not be mixed with any other insulin product.

Carcinogenesis, mutagenesis, impairment of fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog® Mix 70/30. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog®, the rapid-acting component of NovoLog® Mix 70/30, at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog® increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for NovoLog® was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog® was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, *in vivo* micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes. In fertility studies in male and female rats, NovoLog® at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area) had no direct adverse effects on male and female fertility, or on general reproductive performance of animals.

Pregnancy - Teratogenic Effects - Pregnancy Category C

Animal reproduction studies have not been conducted with NovoLog® Mix 70/30. However, reproductive toxicology and teratology studies have been performed with NovoLog® (the rapid-acting component of NovoLog® Mix 70/30) and regular human insulin in rats and rabbits. In these studies, NovoLog® was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of NovoLog® did not differ from those observed with subcutaneous regular human insulin. NovoLog®, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area), and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits based on U/body surface area.

It is not known whether NovoLog® Mix 70/30 can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There are no adequate and well-controlled studies of the use of NovoLog® Mix 70/30 in pregnant women. NovoLog® Mix 70/30 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

It is unknown whether NovoLog® Mix 70/30 is excreted in human milk as is human insulin. There are no adequate and well-controlled studies of the use of NovoLog® Mix 70/30 or NovoLog® in lactating women.

Pediatric use

Safety and effectiveness of NovoLog® Mix 70/30 in children have not been established.

Geriatric use

Clinical studies of NovoLog® Mix 70/30 did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this population.

ADVERSE REACTIONS

Clinical trials comparing NovoLog® Mix 70/30 with Novolin® 70/30 did not demonstrate a difference in frequency of adverse events between the two treatments.

Adverse events commonly associated with human insulin therapy include the following:

Body as whole: Allergic reactions (see PRECAUTIONS, Allergy).

Skin and Appendages: Local injection site reactions or rash or pruritus, as with other insulin therapies, occurred in 7% of all patients on NovoLog® Mix 70/30 and 5% on Novolin® 70/30. Rash led to withdrawal of therapy in <1% of patients on either drug (see PRECAUTIONS, Allergy).

Hypoglycemia: see WARNINGS and PRECAUTIONS.

Other: Small elevations in alkaline phosphatase were observed in patients treated in NovoLog® controlled clinical trials. There have been no clinical consequences of these laboratory findings.

OVERDOSAGE

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

General

Fixed ratio insulins are typically dosed on a twice daily basis, i.e. before breakfast and supper, with each dose intended to cover two meals or a meal and snack. NovoLog® Mix 70/30 is intended only for subcutaneous injection (into the abdominal wall, thigh, or upper arm). NovoLog® Mix 70/30 should not be administered intravenously. The absorption rate of NovoLog® Mix 70/30 from the subcutaneous tissue allows dosing within 15 minutes of meal initiation.

Dose regimens of NovoLog® Mix 70/30 will vary among patients and should be determined by the health care professional familiar with the patient's metabolic needs, eating habits, and other lifestyle variables. As with all insulins, the duration of action may vary according to the dose, injection site, blood flow, temperature, and level of physical activity and conditioning.

Table 3. Summary of pharmacodynamic properties of insulin products (pooled cross-study comparison) and recommended interval between dosing and meal initiation

Insulin Products	**Dose (U/kg) Used in Study**	**Recommended interval between dosing and meal initiation (minutes)***	**Time of Peak Activity (hours after dosing) (mean± SD)**	**Percent of Total Activity Occurring in the First 4 hours (mean, range)**
NovoLog®	0.3	10-20	2.2 ± 0.98	65% ± 11%
Novolin® R	0.2	30	3.3	60% ± 16%
Novolin® 50/50	0.5	30	4.0 ± 0.6	54% ± 12%
NovoLog® Mix 70/30	0.3	10-20	2.4 ± 0.80	45% ± 22%
Novolin® 70/30	0.3	30	4.2 ± 0.39	25% ± 5%
Novolin® N	0.3	n/a	8.0 ± 5.3	21% ±11%

*****Applicable only to Novolin® R and NovoLog® alone or as components of insulin mixes.

Administration using NovoLog Mix 70/30 FlexPen® Prefilled Syringes or vials:

***Disposable NovoLog® Mix 70/30 FlexPen® Prefilled Syringes*:**

NovoLog® Mix 70/30 suspension should be visually inspected and resuspended immediately before use. The resuspended NovoLog® Mix 70/30 must appear uniformly white and cloudy. Before use, roll the disposable NovoLog® Mix 70/30 FlexPen® prefilled syringe between your palms 10 times. This procedure should be carried out with the FlexPen® cartridge in a horizontal position. Thereafter, turn the disposable NovoLog® Mix 70/30 FlexPen® prefilled syringe upside down so that the glass ball moves from one end of the reservoir to the other. Do this at least 10 times. The rolling and turning procedure must be repeated until the suspension appears uniformly white and cloudy. Mixing is easier when the insulin has reached room temperature. Inject immediately. Before each subsequent injection, turn the disposable NovoLog® Mix 70/30 FlexPen® prefilled syringe upside down so that the glass ball moves from one end of the reservoir to the other at least 10 times and until the suspension appears uniformly white and cloudy. Inject immediately. **After use, needles on the disposable NovoLog® Mix 70/30 FlexPen® prefilled syringes should not be recapped. Used syringes, needles, or lancets should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.**

Vial: NovoLog® Mix 70/30 vial must be resuspended immediately before use. Roll the vial gently 10 times in your hand to mix it. This procedure should be carried out with the vial in a horizontal position. The rolling procedure must be repeated until the suspension appears uniformly white and cloudy. Inject immediately.

HOW SUPPLIED

NovoLog® Mix 70/30 is available in the following package sizes: each presentation contains 100 Units of insulin aspart per mL (U-100).

10 mL vials	NDC 0169-3685-12

3 mL NovoLog® Mix 70/30 FlexPen® prefilled syringe	NDC 0169-3696-19

RECOMMENDED STORAGE

NovoLog® Mix 70/30 should be stored between 2°C and 8°C (36°F to 46°F). *Do not freeze*. **Do not use NovoLog® Mix 70/30 if it has been frozen**.

Vials:

The vials should be stored in a refrigerator, not in a freezer. If refrigeration is not possible, the bottle in use can be kept unrefrigerated at room temperature below 30°C (86°F) for up to 28 days, as long as it is kept as cool as possible and away from direct heat and light. Unpunctured vials can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

NovoLog Mix® 70/30 FlexPen® Prefilled Syringes:

Once a NovoLog® Mix 70/30 FlexPen® prefilled syringe is punctured, it may be used for up to 14 days if it is kept at room temperature below 30°C (86°F). NovoLog® Mix 70/30 FlexPen® prefilled syringes in use must NOT be stored in the refrigerator. Keep all disposable NovoLog® Mix 70/30 FlexPen® prefilled syringes away from direct heat and sunlight. Unpunctured NovoLog® Mix 70/30 FlexPen® prefilled syringes can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused NovoLog® Mix 70/30 FlexPen® prefilled syringes in the carton so they will stay clean and protected from light. These storage conditions are summarized in the following table:

	Not in-use (unopened) Room Temperature (below 30°C[86°F])	**Not in-use (unopened) Refrigerated (2°C - 8°C [36°F- 46°F])**	**In-use (opened) Room Temperature (below 30°C[86°F])**
10 mL vial	**28 days**	**Until expiration date**	**28 days (refrigerated/ room temperature)**
3ml FlexPen®	**14 days**	**Until expiration date**	**14 days (Do not refrigerate)**

REFERENCES

1. Raskin R, Allen E, Hollander P, et al. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care*. 2005; 28:260-265.

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Manufactured for:
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Princeton, NJ 08540
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PATIENT INFORMATION

NovoLog® Mix 70/30

(N#-v#-log-MIX-SEV-en-tee-THIR-tee)

(70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin])

Important:

Know your insulin. Do not change the type of insulin you use unless told to do so by your healthcare provider. The amount of insulin you take as well as the best time for you to take your insulin may need to change if you take a different type of insulin.

Make sure you know the type and strength of insulin prescribed for you.

Read the Patient Information that comes with NovoLog Mix 70/30 before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or your treatment.

Make sure you know how to manage your diabetes. Ask your healthcare provider if you have any questions about managing your diabetes.

What is NovoLog Mix 70/30?

NovoLog Mix 70/30 is a man-made insulin that is used to control high blood sugar in adults with diabetes mellitus.

Who should not use NovoLog Mix 70/30?

Do not take NovoLog Mix 70/30 if:

- Your blood sugar is too low (hypoglycemia).
- You are allergic to anything in NovoLog Mix 70/30. See the end of this leaflet for a complete list of ingredients in NovoLog Mix 70/30. Check with your healthcare provider if you are not sure.

Tell your healthcare provider:

- **about all of your medical conditions.** Medical conditions can affect your insulin needs and your dose of NovoLog Mix 70/30.
- **if you are pregnant or breastfeeding.** You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breastfeeding. NovoLog Mix 70/30 has not been studied in pregnant or nursing women.
- **about all medicines you take,** including prescriptions and non-prescription medicines, vitamins and herbal supplements. Your NovoLog Mix 70/30 dose may change if you take other medicines.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare providers when you get a new medicine.

How should I take NovoLog Mix 70/30?

Only use NovoLog Mix 70/30 if it appears uniformly white and cloudy after mixing. There may be air bubbles. This is normal. If it looks clear or if it contains solid particles do not use it and call Novo Nordisk at 1-800-727-6500.

NovoLog Mix 70/30 comes in:

- 10 mL vials (small bottles) for use with syringe
- 3 mL NovoLog Mix 70/30 FlexPen®

Read the instructions for use that come with your NovoLog Mix 70/30 product. Talk to your healthcare provider if you have any questions. Your healthcare provider should show you how to inject NovoLog Mix 70/30 before you start taking it.

- **Take NovoLog Mix 70/30 exactly as prescribed**. You should eat a meal within 15 minutes after using NovoLog Mix 70/30 to avoid low blood sugar.
- **NovoLog Mix 70/30 is a pre-mixed insulin.** The effects of NovoLog Mix 70/30 start working within 15 minutes after injection.
- **Do not inject NovoLog Mix 70/30 if you are not planning to eat within 15 minutes.**
- **Never mix NovoLog Mix 70/30 with other insulin products.**
- **Never use NovoLog Mix 70/30 in an insulin pump.**
- **Inject NovoLog Mix 70/30 into the skin of your stomach area, upper arms, buttocks or upper legs.** NovoLog Mix 70/30 may affect your blood sugar levels sooner if you inject it into the skin of your stomach area. **Never inject NovoLog Mix 70/30 into a vein or into a muscle.**
- **Change (rotate) your injection site within the chosen area (for example, stomach or upper arm) with each dose. Do not inject into the exact same spot for each injection.**
- **If you take too much NovoLog Mix 70/30, your blood sugar may fall low (hypoglycemia).** You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away (fruit juice, sugar candies, or glucose tablets). It is important to treat low blood sugar (hypoglycemia) right away because it could get worse and you could pass out (become unconscious). If you pass out you will need help from another person or emergency medical services right away, and will need treatment with a glucagon injection or treatment at a hospital. See "What are the possible side effects of NovoLog Mix 70/30?" for more information on low blood sugar (hypoglycemia).
- **If you forget to take your dose of NovoLog Mix 70/30, your blood sugar may go too high (hyperglycemia).** If high blood sugar (hyperglycemia) is not treated it can lead to serious problems, like loss of consciousness (passing out), coma or even death. Follow your healthcare provider's instructions for treating high blood sugar. Know your symptoms of high blood sugar which may include:

• increased thirst	• a hard time breathing

• frequent urination	• fruity smell on the breath
• drowsiness	• high amounts of sugar and ketones in your urine
• loss of appetite	• nausea, vomiting (throwing up) or stomach pain

• **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

Your insulin dosage may need to change because of:

• illness	• change in diet
• stress	• change in physical activity or exercise
• other medicines you take	

What should I avoid while using NovoLog Mix 70/30?

• **Alcohol.** Alcohol, including beer and wine, may affect your blood sugar when you take NovoLog Mix 70/30.

• **Driving and operating machinery.** You may have difficulty concentrating or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright to drive if you often have:
• low blood sugar
• decreased or no warning signs of low blood sugar

What are the possible side effects of NovoLog Mix 70/30?

• **low blood sugar (hypoglycemia).** Symptoms of low blood sugar may include:

• sweating	• trouble concentrating or confusion
• dizziness or lightheadedness	• blurred vision
• shakiness	• slurred speech
• hunger	• anxiety, irritability or mood changes
• fast heart beat	• headache
• tingling of lips and tongue	

Severe low blood sugar can cause unconsciousness (passing out), seizures, and death. Know your symptoms of low blood sugar. Follow your healthcare provider's instructions for treating low blood sugar. Talk to your healthcare provider if low blood sugar is a problem for you.

- **Serious allergic reaction (whole body reaction). Get medical help right away, if you develop** a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating.

- **Reactions at the injection site (local allergic reaction).** You may get redness, swelling, and itching at the injection site. If you keep having skin reactions or they are serious talk to your healthcare provider. You may need to stop using NovoLog Mix 70/30 and use a different insulin. Do not inject insulin into skin that is red, swollen, or itchy.

- **Skin thickens or pits at the injection site (lipodystrophy).** Change (rotate) where you inject your insulin to help to prevent these skin changes from happening. Do not inject insulin into this type of skin.

- **Swelling of your hands and feet**

- **Vision changes**

- **Low potassium in your blood (hypokalemia)**

These are not all of the possible side effects from NovoLog Mix 70/30. Ask your healthcare provider or pharmacist for more information.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NovoLog Mix 70/30?

All Unopened NovoLog Mix 70/30:

- **Keep all unopened NovoLog Mix 70/30 in the refrigerator between 36° to 46° F (2° to 8° C).**

- Do not freeze. Do not use NovoLog Mix 70/30 if it has been frozen.

- Keep unopened NovoLog Mix 70/30 in the carton to protect from light.

NovoLog Mix 70/30 in use:

- **Vials**
- Keep in the refrigerator or at room temperature below 86° F (30° C) for up to 28 days.
- Keep vials away from direct heat or light.
- Throw away an opened vial after 28 days of use, even if there is insulin left in the vial.
- Unopened vials can be used until the expiration date on the NovoLog Mix 70/30 label, if the medicine has been stored in a refrigerator.

- **NovoLog Mix 70/30 FlexPen**
- Keep at room temperature below 86° F (30° C) for up to 14 days.
- Do not store a NovoLog Mix 70/30 FlexPen that you are using in the refrigerator.
- Keep NovoLog Mix 70/30 FlexPen away from direct heat or light.
- Throw away a used NovoLog Mix 70/30 FlexPen after 14 days, even if there is insulin left in the syringe.

General advice about NovoLog Mix 70/30

Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use NovoLog Mix 70/30 for a condition for which it was not prescribed. Do not give NovoLog Mix 70/30 to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about NovoLog Mix 70/30. If you would like more information about NovoLog Mix 70/30 or diabetes, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about NovoLog Mix 70/30 that is written for healthcare professionals. Call 1-800-727-6500 or visit www.novonordisk-us.com for more information.

Helpful information for people with diabetes is published by the American Diabetes Association, 1701 N Beauregard Street, Alexandria, VA 22311 and on www.diabetes.org.

NovoLog Mix 70/30 ingredients include:

• insulin aspart	• metacresol

• protamine sulfate	• zinc
• glycerol (NovoLog Mix 70/30 FlexPen only	• disodium hydrogen phosphate dihydrate
• mannitol (NovoLog Mix 70/30 vials only)	• sodium chloride
• phenol	• water for injection
	• hydrochloric acid or sodium hydroxide

All NovoLog Mix 70/30 vials and NovoLog Mix 70/30 FlexPen are latex free.
Date of Issue: November 28, 2008
Version: 6

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

For information about NovoLog Mix 70/30® contact:
Novo Nordisk Inc.
100 College Road West
Princeton, New Jersey 08540

INSTRUCTIONS FOR USE

NovoLog® Mix 70/30 10 mL vial (100 units/mL, U-100)

How should I prepare and deliver the injection using the 10 ml vial?

1. At your first use, remove the tamper-resistant cap of the vial. If the cap has already been removed, do not use this vial and return it to your pharmacy.
2. Wipe the rubber stopper with an alcohol swab.
3. Roll the vial gently 10 times in your hands to mix it. This procedure should be carried out with the vial in a horizontal position. Do not shake it vigorously. Vigorous shaking right before the dose is drawn into the syringe may cause bubbles or froth, which could cause dosage errors. The insulin should be used only if it uniformly appears white and cloudy.
4. Pull back the plunger until the black tip reaches the marking for the number of units you will inject.
5. Push the needle through the rubber stopper into the vial.
6. Push the plunger all the way in. This inserts air into the vial.
7. Turn the vial and syringe upside down together and slowly pull the plunger back to a few units beyond the correct dose.
8. If there are air bubbles in the syringe, tap the syringe gently with your finger to raise the air bubbles to the needle. Then slowly push the plunger to the correct unit marking.
9. Lift the vial off the syringe.

10. Inject right away. If there is a delay after you rolled the vial, you will have to roll it again to remix the insulin. (See injection instructions “How should I inject NovoLog® Mix 70/30 with a syringe)

11. After the injection, remove the needle **without recapping** and dispose of it in a puncture-resistant container. Used syringes, needles, or lancets should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

How should I inject NovoLog® Mix 70/30 insulin with a syringe?

1. Pinch your skin between two fingers, push the needle into the skinfold, and push the plunger to inject the insulin under your skin. The needle should be perpendicular to the skin. This means the needle will be straight in.

2. Keep the needle under your skin for at least 6 seconds to make sure you have injected all the insulin.

3. If blood appears after you pull the needle from your skin, press the injection site lightly with a finger. Do not rub the area.

INSTRUCTIONS FOR USE

NovoLog® Mix 70/30 FlexPen®

Introduction

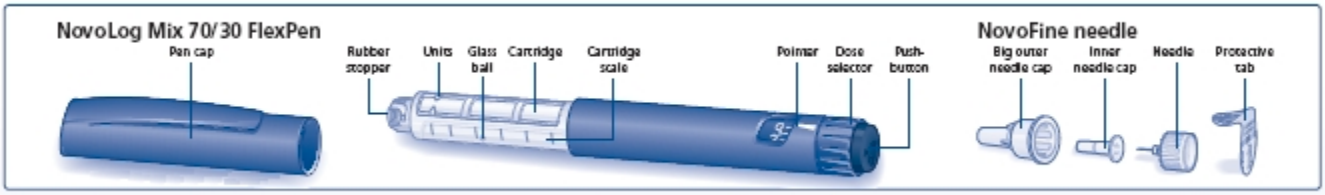
Please read the following instructions carefully before using your NovoLog® Mix 70/30 FlexPen®.
NovoLog Mix 70/30 FlexPen is a disposable dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit.
NovoLog Mix 70/30 FlexPen is designed to be used with NovoFine® needles.

▵ NovoLog Mix 70/30 FlexPen should not be used by people who are blind or have severe visual problems without the help of a person who has good eyesight and who is trained to use the NovoLog Mix 70/30 FlexPen the right way.

Getting ready

Make sure you have the following items:

- NovoLog Mix 70/30 FlexPen
- New NovoFine needle
- Alcohol swab

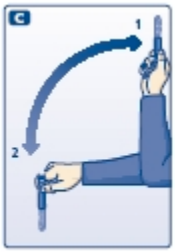


Preparing your NovoLog Mix 70/30 FlexPen

Wash your hands with soap and water. Before you start to prepare your injection, check the label to make sure that you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin. NovoLog Mix 70/30 should look cloudy after mixing. Before your first injection with a new NovoLog Mix 70/30 FlexPen you must mix the insulin:
A. Let the insulin reach room temperature before you use it. This makes it easier to mix.
Pull off the pen cap (see diagram A).

B. Roll the pen between your palms 10 times - it is important that the pen is kept horizontal (see diagram B).

C. Then gently move the pen up and down ten times between position **1** and **2** as shown, so the glass ball moves from one end of the cartridge to the other (see diagram C).



Repeat rolling and moving the pen until the liquid appears uniformly white and cloudy.
For every following injection move the pen up and down between positions 1 and 2 at least ten times until the liquid appears uniformly white and cloudy.
After mixing, complete all the following steps of injection without delay.
Wipe the rubber stopper with an alcohol swab.

▵ Before you inject, there must be at least 12 units of insulin left in the cartridge to make sure the remaining insulin is evenly mixed. If there are less than 12 units left, use a new NovoLog Mix 70/30 FlexPen.

D. Attaching the needle
Remove the protective tab from a disposable needle.
Screw the needle tightly onto your FlexPen. It is important that the needle is put on straight (see diagram D).

Never place a disposable needle on your NovoLog Mix 70/30 FlexPen until you are ready to take your injection.
E. Pull off the big outer needle cap (see diagram E).

F. Pull off the inner needle cap and dispose of it (see diagram F).

▵ Always use a new needle for each injection to help ensure sterility and prevent blocked needles.

▵ Be careful not to bend or damage the needle before use.

▵ To reduce the risk of unexpected needle sticks, never put the inner needle cap back on the needle.

Giving the airshot before each injection
Before each injection small amounts of air may collect in the cartridge during normal use. To avoid injecting air and to ensure proper dosing:
G. Turn the dose selector to select 2 units (see diagram G).

H. Hold your NovoLog Mix 70/30 FlexPen with the needle pointing up. Tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge (see diagram H).

I. Keep the needle pointing upwards, press the push-button all the way in (see diagram I). The dose selector returns to 0.

A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.
If you do not see a drop of insulin after 6 times, do not use the NovoLog Mix 70/30 FlexPen and contact Novo Nordisk at 1-800-727-6500.
A small air bubble may remain at the needle tip, but it will not be injected.

Selecting your dose
Check and make sure that the dose selector is set at 0.
J. Turn the dose selector to the number of units you need to inject. The pointer should line up with your dose.
The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer (see diagram J). When turning the dose selector, be careful not to press the push-button as insulin will come out.

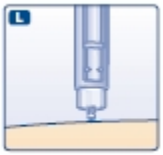
You cannot select a dose larger than the number of units left in the cartridge.
You will hear a click for every single unit dialed. Do not set the dose by counting the number of clicks you hear.

▵ Do not use the cartridge scale printed on the cartridge to measure your dose of insulin.

Giving the injection
Do the injection exactly as shown to you by your healthcare provider. Your healthcare provider should tell you if you need to pinch the skin before injecting.
K. Insert the needle into your skin.

Inject the dose by pressing the push-button all the way in until the 0 lines up with the pointer (see diagram K). Be careful only to push the button when injecting.

Turning the dose selector will not inject insulin.
L. Keep the needle in the skin for at least 6 seconds, and keep the push-button pressed all the way in until the needle has been pulled out from the skin (see diagram L). This will make sure that the full dose has been given.



You may see a drop of NovoLog Mix 70/30 at the needle tip. This is normal and has no effect on the dose you just received. If blood appears after you take the needle out of your skin, press the injection site lightly with a finger. **Do not rub the area.**
After the injection
Do not recap the needle. Recapping can lead to a needle stick injury. Remove the needle from the NovoLog Mix 70/30 FlexPen after each injection. This helps to prevent infection, leakage of insulin, and will help to make sure you inject the right dose of insulin.

▵ Put the needle and any empty NovoLog Mix 70/30 FlexPen or any used NovoLog Mix 70/30 FlexPen still containing insulin in a sharps container or some type of hard plastic or metal container with a screw top such as a detergent bottle or empty coffee can. These containers should be sealed and thrown away the right way. Check with your healthcare provider about the right way to throw away used syringes and needles. There may be local or state laws about how to throw away used needles and syringes. Do not throw away used needles and syringes in household trash or recycling bins.

The NovoLog Mix 70/30 FlexPen prevents the cartridge from being completely emptied. It is designed to deliver 300 units.
M. Put the pen cap on the NovoLog Mix 70/30 FlexPen and store the NovoLog Mix 70/30 FlexPen without the needle attached (see diagram M).

Function Check
N. If your NovoLog Mix 70/30 FlexPen is not working the right way, follow the steps below:
- Screw on a new NovoFine needle.
- Remove the big outer needle cap and the inner needle cap.
- Do an airshot as described in "Giving the airshot before each injection".
- Put the big outer needle cap onto the needle. Do not put on the inner needle cap.
- Turn the dose selector so the dose indicator window shows 20 units.
- Hold the NovoLog Mix 70/30 FlexPen so the needle is pointing down.
- Press the push-button all the way in.

The insulin should fill the lower part of the big outer needle cap (see diagram N). If NovoLog Mix 70/30 FlexPen has released too much or too little insulin, do the function check again. If the same problem happens again, do not use your NovoLog Mix 70/30 FlexPen and contact Novo Nordisk at 1-800-727-6500.

Maintenance
Your FlexPen is designed to work accurately and safely. It must be handled with care. Avoid dropping your FlexPen as it may damage it. If you are concerned that your FlexPen is damaged, use a new one. You can clean the outside of your FlexPen by wiping it with a damp cloth. Do not soak or wash your FlexPen as it may damage it. Do not refill your FlexPen.

- Remove the needle from the NovoLog Mix 70/30 FlexPen after each injection. This helps to ensure sterility, prevent leakage of insulin, and will help to make sure you inject the right dose of insulin for future injections.

- Be careful when handling used needles to avoid needle sticks and transfer of infectious diseases.

- Keep your NovoLog Mix 70/30 FlexPen and needles out of the reach of children.

- Use NovoLog Mix 70/30 FlexPen as directed to treat your diabetes. Needles and NovoLog Mix 70/30 FlexPen must not be shared.

- Always use a new needle for each injection.

- Novo Nordisk is not responsible for harm due to using this insulin pen with products not recommended by Novo Nordisk.

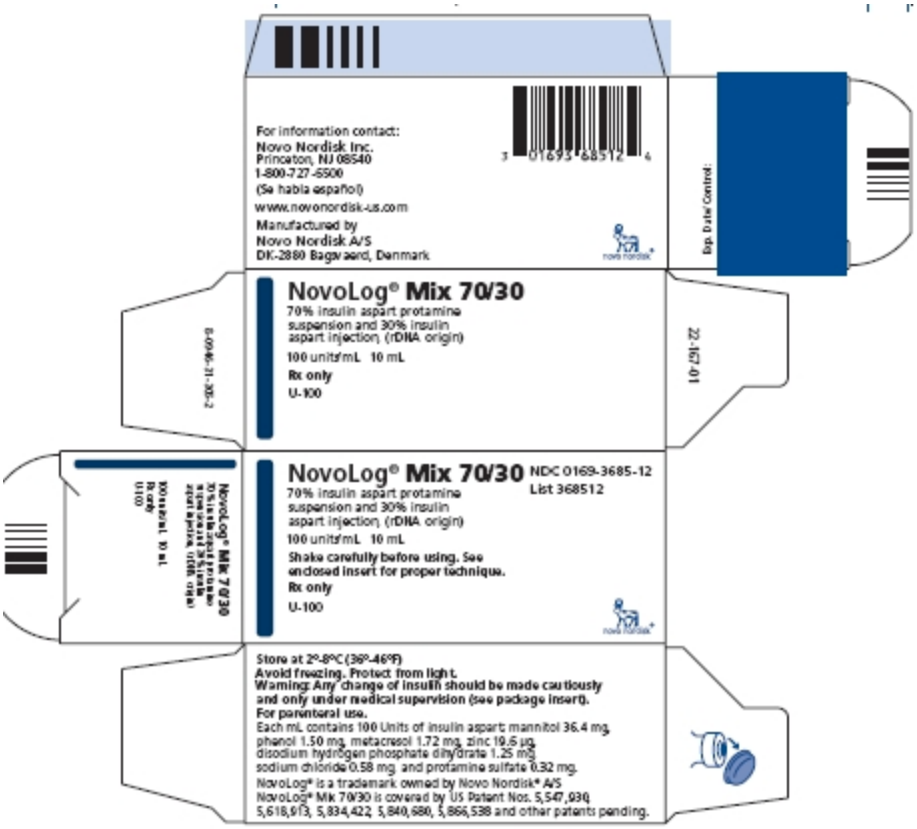
- As a precautionary measure, always carry a spare insulin delivery device in case your NovoLog Mix 70/30 FlexPen is lost or damaged.

- Remember to keep the disposable NovoLog Mix 70/30 FlexPen with you. Do not leave it in a car or other location where it can get too hot or too cold.

PRINCIPAL DISPLAY PANEL
NDC 0169-3696-19
List 369619
NovoLog® Mix 70/30
FlexPen® Prefilled syringe
70% insulin aspart protamine suspension and
30% insulin aspart injection, (rDNA origin)
100 units/mL (U-100)
5x3mL Prefilled Insulin Syringes
Rx only
Single patient use only

Shake carefully before using. See enclosed insert for proper technique.
For use with NovoFine® disposable needles.
Keep in a cold place.
Avoid freezing.
Protect from light.
novo nordisk®

NovoLog® Mix 70/30
NDC 0169-3685-12
List 368512
70% insulin aspart protamine
suspension and 30% insulin
aspart injection, (rDNA origin)
100 units/mL 10mL
Shake carefully before using. See enclosed insert for proper technique.
Rx only
U-100
novo nordisk®



Revised: 10/2009

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